

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/013683

International filing date (day/month/year)
01.12.2004

Priority date (day/month/year)
02.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/403, C07D209/88, C07C203/04, A61P9/12

Applicant
NICOX S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Cortés, J

Telephone No. +49 89 2399-8206



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/013683

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/013683

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-98
	No: Claims	
Inventive step (IS)	Yes: Claims	1-98
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-98
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents have been cited in the International Search Report:

D1: WO 98/21193 A (NICOX) 22 May 1998 (1998-05-22)

D2: EP-A-0 637 583 (PRODESFARMA) 8 February 1995 (1995-02-08)

D3: EP-A-0 200 915 (BOEHRINGER MANNHEIM) 12 November 1986 (1986-11-12)

D4: JAYACHANDRAN ET AL: "Up-regulation of endothelial nitric oxide synthase through beta2-adrenergic receptor: The role of a beta-blocker with NO-releasing action" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 280, no. 3, 2001, pages 589-594, XP002321567

Novelty (Article 33(2) PCT)

The present compounds differ from the compounds in D1 in the definition of the groups R1 and R2 and from the compounds in D2 to D4 in the binding site of the nitrooxy group.

The present compounds are novel.

Inventive Step (Article 33(3) PCT)

D1 discloses nitrooxy derivatives of the beta-blocker timolol. D2 discloses nitrooxy derivatives of the beta-blockers propranolol, metoprolol and atenolol. D3 discloses beta-blockers which are carbazol-nitrooxy derivatives. D4 discloses the beta-blocker nipradilol which has a nitrooxy function.

D1 could be regarded as the closest prior art.

The problem of the invention was the provision of new beta-blockers with an improved pharmacology.

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/013683

The Applicant has demonstrated by means of a comparative assay that nitrooxy derivatives of carvedilol have an effect on the cGMP accumulation in cells.

This specific pharmacological effect is not suggested for the present compounds by none of the cited documents neither alone or in combination.

The present invention is therefore based on an inventive step.